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BIOLOGICAL BULLETIN

IMMUNITY AND ADAPTATION.[1]

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Various writers, in discussing the phenomena of adaptation, included among them the fact that in many cases organisms become immune against certain injurious influences, as for instance the action of toxic substances, provided that these influences were active during a sufficiently long period; the immunity against disease-producing bacteria was especially regarded as a phenomenon of adaptation. These writers, therefore, explained immunity by including it among the larger class of adaptive phenomena. Although this attitude appears from a certain point of view as the most rational one, it may nevertheless in other respects be more fruitful to adopt the opposite attitude, which consists in trying to gain an insight into the mechanism of certain adaptive phenomena, by making use of the discoveries made in the course of investigations in immunity. This attitude seems also justified by the fact that a large number of instances of acquired immunity cannot be directly explained as adaptive phenomena. In these respects, therefore, the conception of immunity is wider than that of adaptation.[2] The main reason for taking the second attitude, however, lies in the fact that the phenomena of immunity have been partially at least accessible to an experimental analysis, much more so than other phenomena of adaptation.

The latter may be conveniently classified as internal and ex-

[1] From the Pathological Laboratory of the University of Pennsylvania.

[2] T. H. Morgan in his book on "Evolution and Adaptation" includes the phenomena of immunity among the adaptive processes. He expresses, however, the view that certain of these phenomena could not be explained as due to any selective processes. The following remarks, the partly hypothetical character of which is quite apparent, were written with the aim of connecting a number of somewhat isolated facts, and of suggesting the possibility of an extension of such considerations to different fields of investigation.

ternal, as adaptations of one part of the body to another part of the same organism and adaptations of an organism or of one of its constituent parts to the outer world, although these two kinds of adaptations must not necessarily be regarded as sharply distinct, inasmuch as it can be assumed that external conditions cause a primary internal reaction, which gives rise to a secondary internal change, the latter possessing the character of an adaptation and therefore representing directly an internal, indirectly however an external adaptation.

It appears possible to connect certain characters, whose usefulness for the organism possessing them, seems to justify their classification among the adaptive phenomena with other facts which have been found by the experimental study of immunity. A few adaptations of this kind may be selected to demonstrate this connection. In the tissues of vertebrates and invertebrates, substances are present which have a strongly accelerating effect upon the coagulation of the blood. If a wound is made and the blood escapes, the contact with these tissues has a tendency to stop the bleeding and prevent the animal from bleeding to death. The tissues of each class of animals are especially adapted to the fibrinogen of their own blood. The blood of a bird coagulates more quickly under the influence of the tissue of a bird than of a dog or of a frog. The blood of a turtle coagulates more quickly under the influence of the tissues of a turtle than of the tissues of a mammal or of a bird. The same holds good of frogs' blood. Invertebrate blood, like that of a lobster, is not at all influenced by the tissues of vertebrates, but very powerfully so by the tissues of the lobster and to a less degree by the tissues of some other invertebrates. Here we have apparently to deal with a specific adaptation. A certain relationship exists between blood and tissues of one class of animals; a specific relationship, which proves very beneficial to the animal. A somewhat analogous fact is mentioned by Duclaux. He states that it is well known to manufacturers of dairy products that the milk of a certain species of animals is more rapidly coagulated by the rennin of the same than of another species.[1]

[1] Although the analogy between these two facts is clear, the usefulness apparent in the case of the tissue coagulins, seems to be absent in the case of the specificity of rennin. The latter fact can therefore not be included among the phenomena of adaptation.

Certain parasitic animals, as the leech and anchylostoma, live entirely or partially by taking into their digestive system the blood of the host. In regard to anchylostoma it is not quite certain whether it sucks the blood of the host directly or whether it obtains the blood together with parts of the mucous membrane of the internal canal which it inhabits. Blood of the host certainly forms an important part of the food of the parasite. Both of these worms contain in the anterior part of their body, substances which strongly inhibit the coagulation of the blood. Thus the blood is kept in a liquid state and the sucking of the blood and probably also its digestion and resorption are rendered much easier. This was demonstrated in the case of the leech many years ago by Haycraft and recently also in the case of anchylostoma. Here again we have to deal with a process which to some degree is specific, inasmuch as the substance which has such a powerful action in inhibiting the coagulation of the blood of the host is absolutely without influence on the coagulation of invertebrate blood. And there are even certain indications tending to show that this substance does not act equally strongly on all vertebrate blood, inasmuch as Sabbatani found that a similar substance in another blood-sucking animal, ixodes ricinus, acts much more strongly on dog blood, the blood which is sucked by this tick, than on rabbits' blood. I myself found in one experiment made that the substance which is present in anchylostoma, inhibiting the coagulation of the blood of the dog, was powerless towards the blood of guinea pigs.[1]

The fact that leech extract is without effect on the blood of the lobster makes it furthermore more probable that it is also without power upon the blood of the leech itself.

Snake venom, a most powerful poison for many vertebrates, is almost harmless for snakes, themselves. This is as Phisalix found at least partially due to the presence of an antitoxin in the blood of the snakes. The blood of these animals may therefore contain toxin and antitoxin side by side. This immunity of snakes against their own poison is of great significance, otherwise an injury of their tongue or any other part of their body by the teeth of the animal would be fatal.

A toxin similar to snake venom is contained in the abdominal

[1] This experiment needs to be repeated.

segments of scorpions. The scorpions possess, as Metschnikoff describes, in their blood an antitoxin against scorpion venom, which is very poisonous for other insects and to vertebrates. Certain desert animals are frequently exposed to the bite of scorpions, and in accordance with this fact, it has been recently found that such animals are not susceptible to this poison, although other animals nearly related to the desert animals, but not living in localities where they are exposed to bites of scorpions, are easily poisoned. Whether the blood of these animals has any antitoxic action, does not yet seem to have been determined.

For a long time an explanation had been sought for the fact that the mucous membrane is not digested by the pepsin and hydrochloric acid, which are secreted by the cells of the mucous membrane. Recently Weinland has shown that the cells of the mucous membrane of the stomach contain a substance able to neutralize the action of the digestive ferment, an antipepsin. Although it is not certain or perhaps even unlikely that the presence of this substance is sufficient to account in itself for the power of resistance shown by the cells of the mucous membrane, yet it represents in all probability at least one important contributing factor and is therefore a cellular adaptation, without which life would be impossible.[1]

In the course of the study of the action of bacteria and their toxins on the animal organism, it has been found that injection of bacteria into the body of an animal may cause in the serum of the injected animal the appearance of substances, which produce an agglutination or even a solution of the bacteria (agglutinins, bacteriolysins). Injections of bacterial toxins may produce the appearance of antitoxin in the serum. Later it was found that this response of the animal organism was not limited to bacteria and their products but was also present in the case of injections of animal and plant cells in general and even of ferments and albuminous substances. The substances which after a certain period are to be found in the blood serum have all this in common that in some way they antagonize the organisms or substances, which had been injected and which had caused the appearance of the reactive substances. The way in which this antagonizing effect does take place is different in different cases.

[1] Metschnikoff; "L'immunité," Paris, 1901. Chapter XI.

Some facts are known in regard to the place of origin of such "antibodies" and in regard to the conditions which favor or inhibit their appearance. From a certain point of view we may at present perhaps distinguish three types of reactions.

1. If at certain intervals a solution of abrin is dropped into the conjunctival sac of an animal, substances are formed in the conjunctiva to which the abrin was applied, which are able to neutralize the injurious effect of abrin. In this case a local response of the cells on which the substance acted, has taken place.

2. If we inject substances, as cultures of the cholera vibrio subcutaneously, intraperitoneally or intravenously, antibodies are produced in organs far removed from the place of injection, as for instance in the spleen and in the bone-marrow. The mere injection of these substances is sufficient to produce this result.

3. There exists a third type of reaction, which seems to be of a more complicated character than the forementioned ones, and which hitherto has been regarded as a totally different process, but which seems to be essentially of a similar character. The normal pancreas, which is the source of several hydrolytic ferments usually does not produce lactase, a ferment capable of splitting the disaccharid lactose. If, however, an animal receives with its food a certain quantity of lactose, for instance in the form of milk, lactase is secreted by the pancreas. The introduction of a carbohydrate into the animal body causes, therefore, in this case the appearance of a specific substance able to destroy the carbohydrate. The lactase may be called an antibody. If we inject, however, lactose directly into the blood, lactase is not produced. The mechanism of the production of this substance seems to have been in the main cleared up by Bayliss and Starling and Bainbridge. It appears that through the introduction of lactose into the alimentary canal a substance is formed in the mucous membrane of the small intestine, which gradually passes into the circulation and causes the pancreas to secrete the lactase. It is possible to extract this substance from the intestines in vitro and to cause a secretion of lactase by injecting the extract into a vein. In this case it is not the original substance itself which by passing into the circulation causes directly the appearance of an antibody, but it is a second substance formed under

the influence of the lactose in the cells, with which the lactose or component parts of the lactose comes into contact.[1]

The difference between the second and third mode of action is not of such a character as to render it impossible to regard the latter as related to the former, especially as we do not know whether intermediary processes do not also take place even in those reactions, which are included under the second type. It is not impossible that a similar complicated character will be shown to exist in some reactions in the second class, which have been regarded as direct ones.

The presence of antibodies can, however, not always be demonstrated in cases of artificially produced immunity. It has for instance been impossible to obtain antibodies after injection of certain chemical substances, which are of a less complicated character than the albuminous substances mentioned above, *e. g.* certain alkaloids.

If we now turn again to the adaptations, which were mentioned above as occurring naturally, it is not difficult to see that a great similarity exists between the natural and the experimental reactions. The existence of an antipepsin in the mucous membrane of the stomach seems analogous to the production of antiabrin in the conjunctiva. In both cases we have to deal with an apparently local production of an antibody. If we find in scorpions and in snakes an antibody against their own venom circulating in their blood, it is not unlikely that we have to deal with a reaction of the second class. The fact of the leech and ankylostoma producing substances inhibiting the coagulation of the kind of blood they swallow may with some probability be classed among the reactions of the third type. The same probably holds good for the tissue coagulins. Whether in the case of the desert animals an antibody is present does not seem to have been determined; it is, therefore, possible that we might have to deal with an acquired immunity without the presence of an antibody which can be demonstrated. On the other hand it is not unlikely that further investigation will show the existence of an antitoxin.

Plausible as the explanation given of some of these adaptations, as experiments of nature in immunity may appear, there seems

[1] The deductions of Starling and Bainbridge have recently been controverted by Bierry.

to be some objection to applying it to cases in which the substance causing the immunization or adaptation is derived from the same animal in which the antibody is produced. Antibodies have been experimentally produced only in such cases in which certain substances derived from one animal were injected into another animal and usually those belonging to a different species. The experimental proof has, however, been given that in certain cases iso-antibodies can be produced, by the injection of animal cells or animal products into other animals of the same species. Furthermore it could be shown that such antibodies may act not only on the cells of another animal of the same species but even on the analogous cells of its own body. This for instance was found in the case of the spermotoxins. An antibody against its own spermatozoa can be produced in the same animal which has been injected with spermatozoa of another animal of the same species. Whether the spermatozoa are able to produce antibodies if they are injected into the same animal from which they are derived, has apparently not yet been investigated; but it appears not unlikely that it might succeed. Such an experiment gave negative results in the case of the blood cells which are however normally circulating in the blood. Certain other facts point to the conclusion that such autoantibodies may be formed without experimental interference under natural pathological and even normal conditions. If one kidney becomes chronically diseased by experimental interference so that tissue of the kidney is being resorbed, the serum seems to assume properties, injurious to kidney tissue of the same animal. If we inject such serum into the circulation of another animal of the same species, albuminuria appears as a sign that the kidneys have been injured. Even if this observation should be open to a different interpretation, there are other facts which suggest a similar conclusion. It is certain that such digestive ferments as trypsin pass normally into the circulation and may be excreted by the kidney. As might be expected from what has been said before, an antitrypsin exists in the serum, or the serum has antitryptic properties, just as the snake blood contains antitoxin against snake venon.

Glaessner found even that the tryptic power of the serum varies

at different periods of the day and that these variations indicate a certain relationship to the time at which the food is taken in and at which trypsin is secreted. This is very suggestive of the rapid formation of an antibody in response to the normal increase of a certain ferment in the circulation. In a similar way the blood serum of a horse and a pig was found by Briot, Roden and Korschun to contain normally an antibody against rennin. This natural antibody acts in the same way as the one experimentally produced by injecting rennin into other animals, probably combining with the rennin. A further observation strengthening the evidence that autoimmunizatory processes may take place is that during the puerperium an increase of isoagglutinins takes place in the human body. This is probably the result of the resorption of substances from the uterus and other organs. The resorption of these substances seems to modify the action of the blood serum on the blood cells of the same species of animals.

The specific character of the experimentally produced antibodies is quite marked; these antibodies possess a certain relationship to that substance whose introduction into the animal organism caused the antibody to appear. This specificity is of a twofold character. In the first place the antibody reacts only against a chemical substance similar in composition to the one which caused it to originate, secondly there exists a species specificity. Substances apparently equally constituted, but derived from different species, behave differently towards the antibody, those substances showing the strongest reaction which are derived from the same species, or from a species similar to the one from which the substance was obtained whose introduction into an animal organism caused the formation of the antibody. The latter (and also the former) kind of specificity is not absolute, substances derived from nearly related species showing a similar although usually a weaker reaction.

Such a specificity may also be noticed in the adaptations described above. The snake and scorpion antitoxin are specific for snake and scorpion toxin respectively. The leech extract is without effect on the plasma of invertebrates, but acts only on the plasma of vertebrates; in the case of ixodes and anchylostoma, the specificity may perhaps even go farther, so that the

antiferment acts mainly on the blood of that species which is sucked by the parasite. In regard to the tissue coagulins, their specificity has already been mentioned above. We might be able to distinguish by the aid of this specificity for instance the muscle of a lobster from that of a blue crab. In the whole, however, we have to deal here rather with a class specificity than with a species specificity. The specificity is not so strongly pronounced in the case of the naturally produced antibodies as in those cases in which antibodies are produced artificially. Glaessner believes that a specificity of the antitrypsin of the blood exists even among different mammalians. The number of his experiments seems, however, to be very limited, so that at present this specificity cannot yet be accepted as proven. It is possible that also in this case a class specificity does exist rather than a species specificity. This may also apply to enterokinase, which activates trypsinogen. A species specificity does not seem to exist in this case, but a class specificity may nevertheless be present.

Both classes of substances, the experimentally produced, as well as the naturally occurring substances, are specific, not only in the sense that they are chemically different from substances found elsewhere but that they have a specific relationship to the substance which caused their appearance and that they indicate the species or class origin of this latter. Their action is, therefore, a selective one and they are not only specific in the sense of being chemically different from other substances but they are specifically adapted to a certain action on a very limited number of substances. We may, therefore, call these substances "specifically adapted" substances.

We suggested that the tissue coagulins owe their origin to a process of autoimmunization, the character of a certain fibrinogen determining the character of the coagulins of the same species or class. Tissue coagulins resemble very closely enzymes. The secretion of lactase, a typical ferment, is, as we saw, due to the introduction of lactose into the organism. This suggests that other ferments have a similar origin; they may be regarded as antibodies produced by a complex process of autoimmunization. The existence and interaction of ferments in the animal organism is perhaps the most perfect instance of internal adaptation.

So far we had only to deal with chemical not with structural adaptations. It seems, however, possible to extend the preceding considerations to structural adaptations. Ferments produce primarily chemical changes. But we know of chemical ferment actions which bring about structural changes in the medium in which they act. Thrombin in transforming fibrinogen into fibrin changes a colloidal fluid into a gelatinous more or less solid mass, which under the influence of pressure and traction may show a fibrillar structure not unlikely connective tissue. From a certain point of view, the fibrin ferment may, therefore, be regarded as a form producing ferment.[1] We might call it a morphogenic ferment. We have reason to assume that there exist other morphogenic ferments. So far mainly the splitting activity of ferments has been studied. It is not unlikely that the action of many enzymes may be reversible. There would then exist a large number of enzymatic actions, leading to the building up of complicated chemical compounds from relatively simple substances. Such an action would probably in part again be connected with the creation of definite structures, which would be different under the influence of different enzymes. These enzymes would have a specific species, and also a specific individual character and the analogous products created by such ferments would be different in different species and in different individuals.

Such an interaction of substances with the resulting formation of antibodies could especially be conceived of as taking place during embryonic development; it would tend to produce a correlation between different chemical and structural mechanisms which might in part at least account for the harmony which exists in the function and structure of different parts of an organism.

It has not yet been investigated as far as I am aware, whether some of the adaptations mentioned above have been acquired in each individual or whether they are hereditary. That might be doubtful, especially for instance in the case of the immunity of scorpions and snakes against their own venom. The latter alternative is, however, very likely in the case of the anticoagulative substance of the leech and of anchylostoma and in the case

[1] The fact that the fibrin ferment produces organized substance has already been noted by Gautier.

of the tissue coagulins. It might be of interest to examine the existence of such a substance in leeches which had never had an opportunity of sucking blood containing an active thrombin, *e.g.*, of leeches which had been nourished on blood which had been previously heated to 56°, and to investigate whether the desert animals raised at places where they are exempt from scorpion bites, would nevertheless develop immunity against scorpion bites.

If a hereditary fixation of the production of an antibody should take place, then such a substance could be formed independently of the presence of the substance which originally caused its production and the origin of such an adaptation would, if regarded as an isolated fact, not be apparent.

In connecting these different facts it was intended to show the analogy existing between several adaptations which are probably fixed by heredity and certain reactions of the animal organism which can be produced experimentally. If we shall be able to clear up more and more the phenomena of experimental immunization we may hope to explain by the same studies, one factor which seems to form an essential part of many adaptations.

Most of the reactions considered so far are useful for the organism in which the reaction is taking place. It is, however, possible to produce experimentally reactions of a similar character, in which no useful result can be recognized. It is furthermore not unlikely that the same principle (the formation of antibodies) may under certain naturally occurring circumstances lead to conditions which are injurious to the animal organism, as in the case of destructive processes taking place in one kidney. Uremia is explained by Ascoli through the formation of nephrolysins. It has been thought possible to explain on a similar basis through the formation of syncytiolysins conditions of such an acute pathological character as eclampsia. How far these views are correct, it is at present impossible to determine. The possibility must, however, be conceded that the same principle underlies equally very striking adaptations and somewhat less apparent disease producing processes. In recognizing this it will be easier to apply to the phenomena of adaptation the same causative investigation as to other phenomena.